Unmet needs in clinical endpoints and therapeutics for retinal diseases: challenges and innovations

Glaucoma and retinal ganglion cell neuroprotection as a case study

Forward Looking Statements

This release contains "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, Section 21E of the Securities Exchange Act of 1934 and the Private Securities Litigation Reform Act of 1995. These forward-looking statements are not based on historical fact and include statements regarding: the potential benefits of tarcocimab; the ABC platform science continuing to advance a next set of investigational therapies for high prevalence retinal diseases; and the advancement and potential of the VETi program. Forward-looking statements generally include statements that are predictive in nature and depend upon or refer to future events or conditions, and include words such as "may," "will," "should," "would," "could," "expect," "plan," "believe," "intend," "pursue," and other similar expressions among others. Any forward-looking statements are based on management's current expectations of future events and are subject to risks and uncertainties that could cause actual results to differ materially and adversely from those in or implied by such forward-looking statements. For a discussion of risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in our most recent periodic report filed with the U.S. Securities and Exchange Commission (“SEC”) as well as discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the SEC. These forward-looking statements speak only as of the date hereof and Kodiak undertakes no obligation to update forward-looking statements, and readers are cautioned not to place undue reliance on such forward-looking statements.

Chemistry meets ophthalmology

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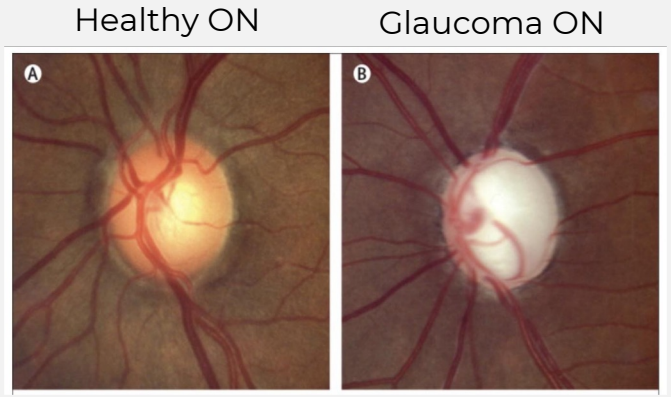
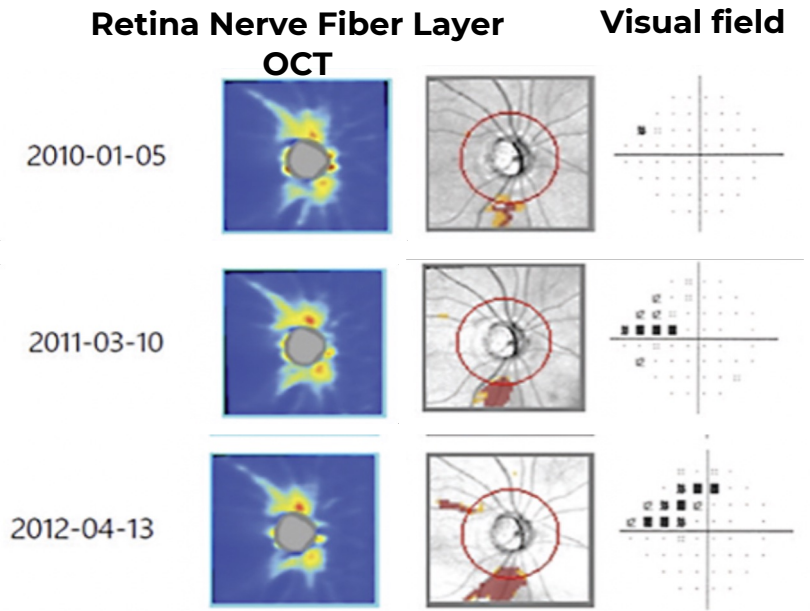
Glaucoma is a group of progressive optic neuropathies characterized by retinal ganglion cell (RGC) degeneration and optic nerve (ON) damage

Glaucoma is characterized by RGC degeneration and changes in the optic nerve head (its axons)



- Glaucoma globally affects 3.5% of the population over 40 years old (76M WW, 3M US)
- Cumulative incidence of blindness is 33% in 10 years

In the clinic, glaucoma progression is tracked using OCT (structural) and visual field (functional) measures



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Lancet. 2011 Apr 16;377(9774):1367-77; Ophthalmology 2014 Nov;121(11):2081-90
RNFL: Retinal Nerve Fiber Layer

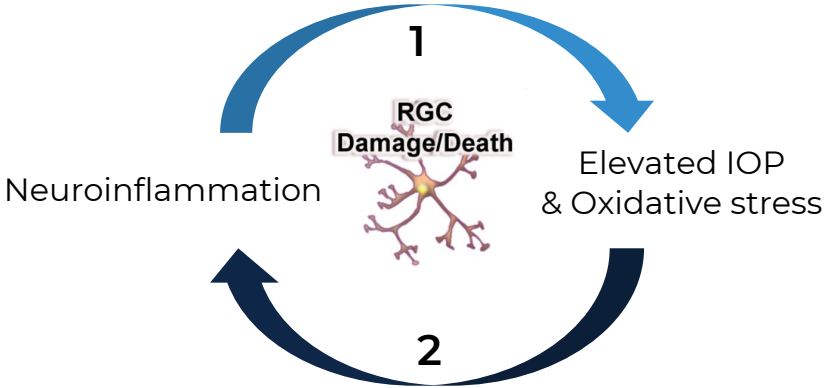
Glaucoma is an optic neuropathy driven by neuroinflammation—IOP reduction alone is insufficient

- **Historically, glaucoma was thought to occur *due to* elevated IOP**
  - Raised IOP was thought to inflict damage on the ONH via mechanical stress
  - Reduction of IOP is known to mitigate glaucoma progression
- **However, data suggest that an IOP-independent mechanism is at play**
  - Many people with high IOP do not develop glaucoma
  - 30-40% of patients with glaucoma present with normal or low IOP. Many continue to experience vision loss due to glaucoma progression[1]

IOP: intraocular pressure; ONH: optic nerve head; RGC: retinal ganglion cell

1. Coyle S, et al. Targeting the NLRP3 Inflammasome in Glaucoma. Biomolecules. 2021 Aug 19;11(8):1239. doi: 10.3390/biom11081239. PMID: 34439904; PMCID: PMC8393362. 2. Adornetto et al. Neur Regen Res 19

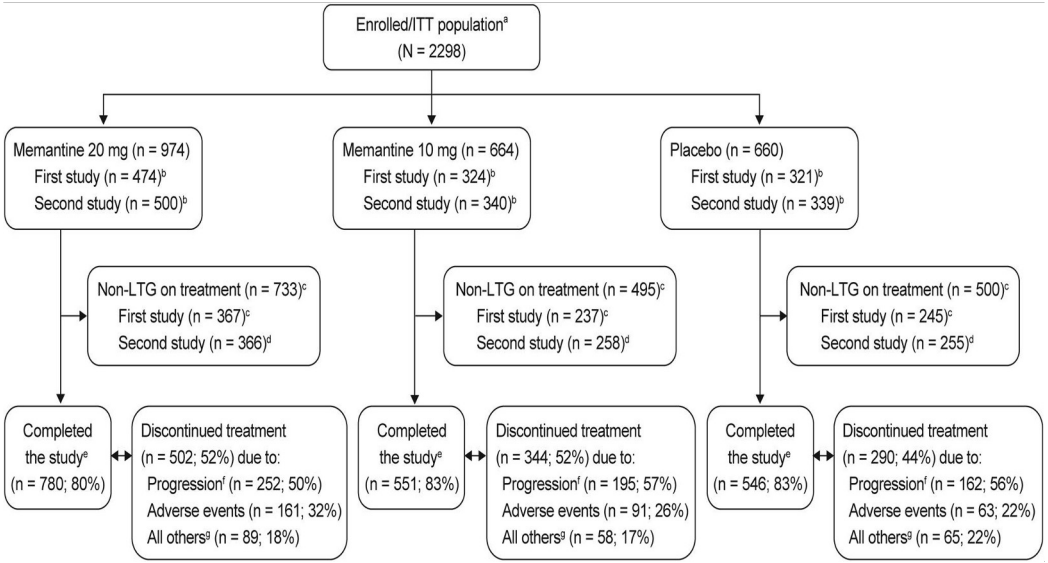
Recent studies show that neuroinflammation is the key driver of optic neuropathy in glaucoma[2]



- Current therapies focus on lowering IOP as it is the only modifiable risk factor
- **There is an unmet need to develop new therapies that target the underlying neuroinflammation that drives optic neuropathy**

However, memantine experience highlights the difficulty in conducting neuroprotection studies

Two phase 3 trials (n=2298); primary endpoint-visual field progression over 48 months, with decade-long duration



Key challenges:

- Slow and prolonged disease course
- Variable progression rates among patients
- High variability in visual field measurements
- Need to test neuroprotective agent on top of standard of care (IOP lowering eyedrops)

ClinicalTrials.gov identifiers, NCT00141882 and NCT00168350; Ophthalmology. 2018 Dec;125(12):1874-1885.

Can adequate and well controlled trials be designed to study glaucoma neuroprotection?

FDA guidelines for an adequate and well controlled trial:

Study design permits **valid comparison**	**Minimize bias** on part of subjects, observers and analysts	Method of **assessment** is well defined and **reliable**
Comparator arms should have similar dosing schedules and evaluation timepoints	Randomization and masking of treatment arms	Endpoints which are important to subjects

Transl Vis Sci Technol. 2023;12(11):33; Transl Vis Sci Technol. 2025;14(7):11

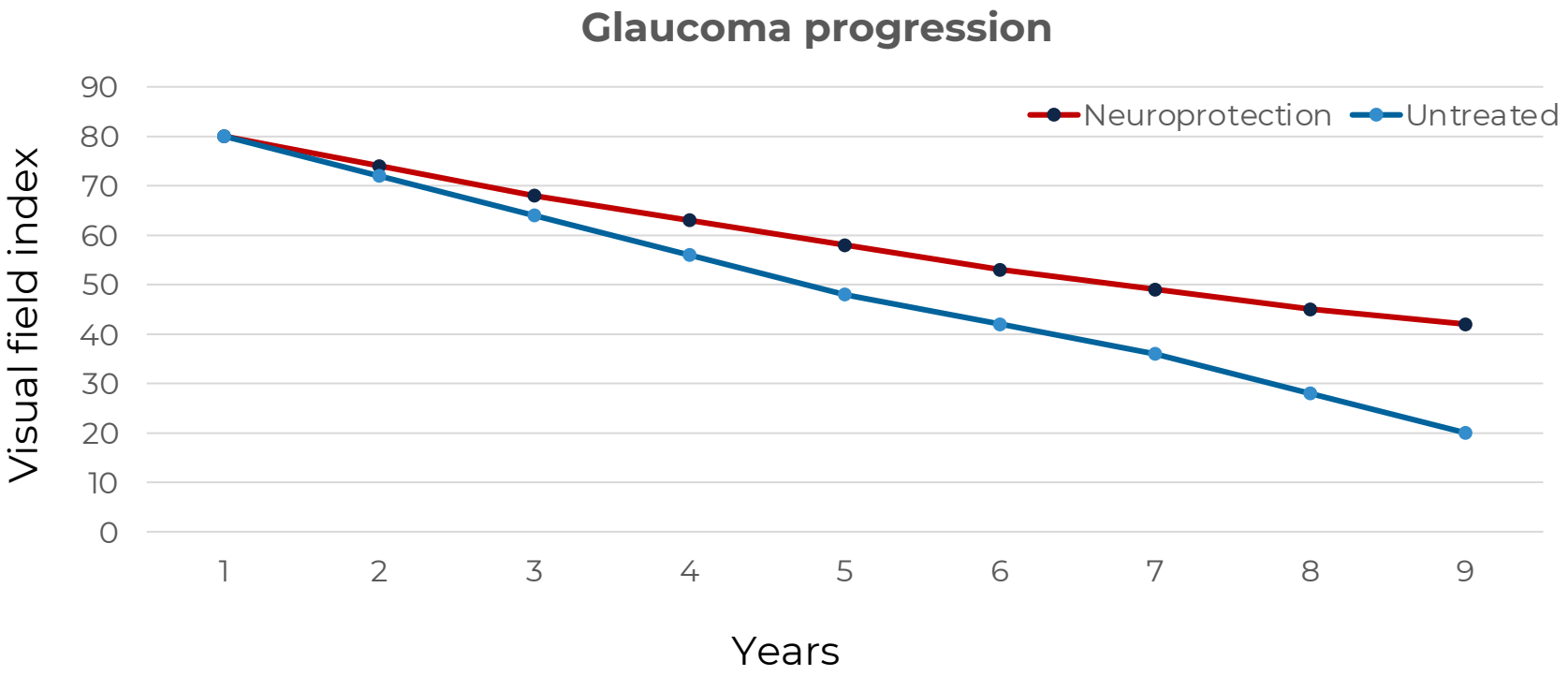
Achieving clinically meaningful and approvable endpoints in glaucoma neuroprotection is challenging today

Study design permits **valid comparis**	**Minimize bias** on part of subjects, observer and analyst	Method of **assessment** is well defined and **reliable**
Comparator ms should have similar dosing schedules and evaluation timepoints	Randomiza and masking of treatment arms	Endpoints which are important to subjects

Glaucoma clinical endpoints	Currently studied
Prevention of nerve fiber layer thinning (via RGC loss)	No
Visual field (mean ≥ 7dB in an area consisting of at least 5 points)	No
IOP reduction	Yes

- Nerve fiber loss and visual field are the two clinically meaningful endpoints in glaucoma neuroprotection
- No therapy has demonstrated preservation
- Bar for clinical trials to show this level of superiority is very high

Old thinking: neuroprotection takes a long time to measure



Illustrative only

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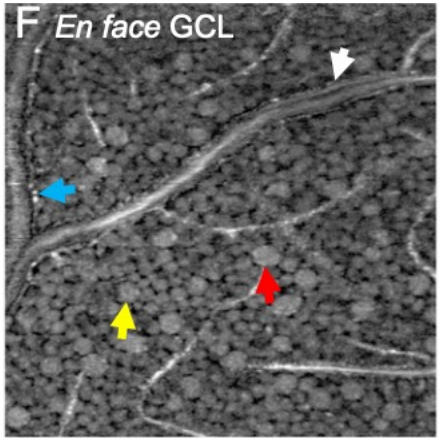
New thinking: improving clinical trial endpoints in glaucoma neuroprotection

More frequent testing to minimize visual field variability

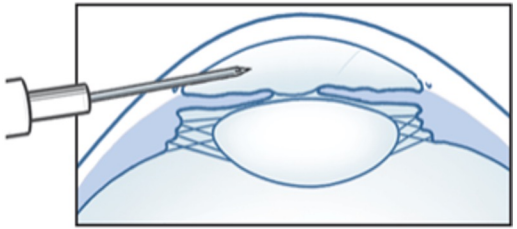
Sample size can be reduced by 40% with a cluster testing paradigm[1,2]

Greater sensitivity for detecting retinal ganglion cell (RGC) losses



Enable direct visualization of RGC at a cellular level[3]

Early activity biomarkers

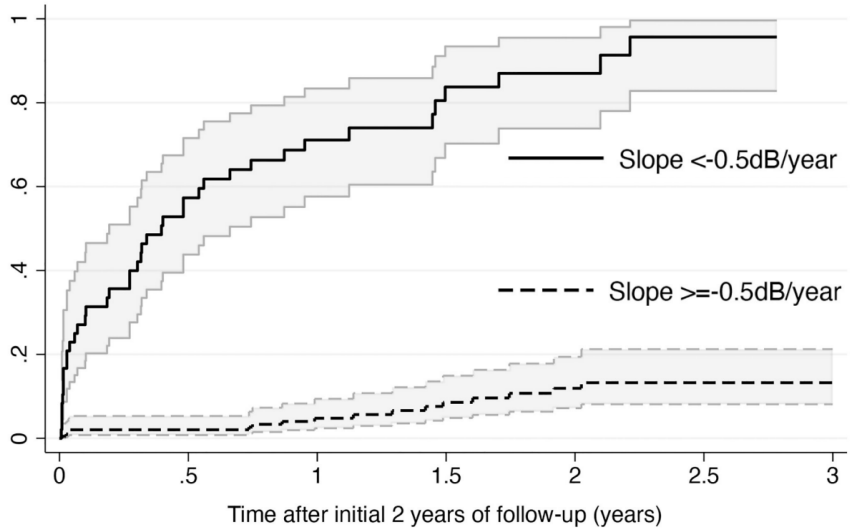


Neurofilament light chain (NFL), a neurodegeneration biomarker, is elevated in glaucoma patients' aqueous humor and could potentially indicate early neuroprotective drug activity[4,5]

1. Wu & Medeiros. Scientific reports (2018) 8:4889 2. Transl Vis Sci Technol. 2024 Jun 3;13(6):14. 3. Proc Natl Acad Sci U S A. 2017 Nov 28;114(48):12803-12808 4. Transl Vis Sci Technol. 2025 Feb 3;14(2):24 5. IOVS June 2025, Vol.66, 4005

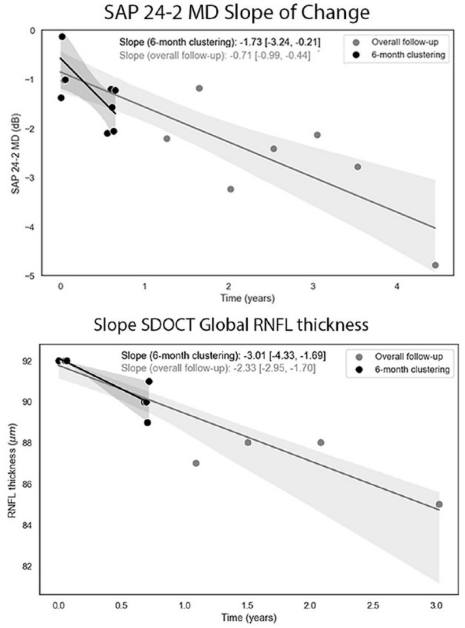
New thinking: reducing the sample size by selecting fast progressors

Fast progressors have a higher likelihood of meeting FDA event criteria



- Eyes with faster progression are much more likely to develop a clinical endpoint: 98% versus only 14% over 3 years.
- Sample size can be reduced from 495 to 182 per arm when the progression rate increases from 0.54 dB/year to 1.56 dB/year (30% treatment effect assumed)

Six-month run-in predicts future progression—feasible for clinical trials



Curr Opin Ophthalmol. 2012 Mar;23(2):144-54. Ophthalmology. 2023 May;130(5):469-477. Ophthalmology. 2024 Jun;131(6):645-657.

Remaining challenges in developing a glaucoma neuroprotection drug

- **Standard of care constraints:** Withdrawing IOP-lowering drops is unethical, so new therapies must demonstrate neuroprotection on top of existing treatments
- **Multifactorial disease:** Glaucoma optic neuropathy involves multiple pathogenic pathways, often requiring a polymedicine approach. Combining dual mechanisms in a single therapy could address this complexity
- **Drug delivery challenges:** Neuroprotection targets are mostly intracellular, making retinal ganglion cell delivery of small molecules difficult. Durability is critical, as frequent dosing is impractical; quarterly delivery is preferred over daily drops
- **Adherence and treatment burden:** Less frequent dosing improves adherence, but achieving durable, effective concentrations in the retina remains a key challenge

Therapeutic innovation is needed to overcome these challenges

—a therapy that can combine multiple mechanisms of action, target retinal ganglion cells directly, and provide long-term durability

Applying the ABCD Platform to Glaucoma

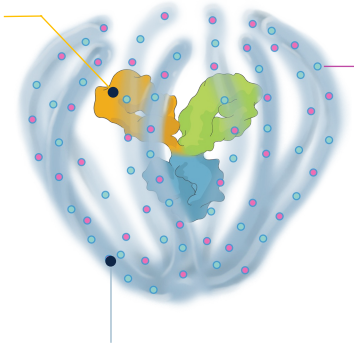
Kodiak's ABCD Platform is designed for targeted, high drug loading, multi-specific and tailored modulation of biological pathways

Antibody Biopolymer Conjugate Drug ("ABCD"):

A product platform enabling multi-mechanism therapies empowered for durability

Antibody or other Biologic

Any biologic can be conjugated to the biopolymer via a stable, site-specific linkage



Drug Cargo

Diverse APIs of varying biophysical properties are covalently embedded in the biopolymer and released over a designed-in time

Biopolymer

Engineered to make medicines last longer and extend their therapeutic benefit. Combines multiple APIs and can be tailored to meet a specific therapeutic goal. High molecular weight, optically clear and made of phosphorylcholine, the primary hydrophilic component of human cell membranes

Conjugates of diverse APIs +/- a biologic
Target both intracellular and extracellular pathways

High Drug Antibody Ratio ("DAR") medicines
Can include APIs with DAR of 10 up to >250

Tailored release of APIs
Release of API payloads enabled by pH modulation or enzymatic cleavage of linkers

Proven safety record of the ABC Platform
>2,500 patient years of experience in patients and >13,00 tarcocimab injections

A new combination of targeting, high drug loading, mixed API formats and tailored drug release – with applications in ophthalmic and systemic diseases

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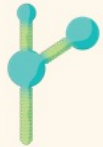
The ABCD Platform is modular and each component can be customized to fit a specific therapeutic need

Antibody or Other Biologic

Antibody

Fusion Protein



Aptamer

Biopolymer

(Copolymer is customizable to match therapeutic need)

9-arm

- 10% drug loading
- 500 or 750kD
- DAR of 166 or 250

3-arm

- 3% or 10% drug loading
- 150 or 250kD
- DAR of 15 or 83
- +/- conjugation snout for conjugation to a biologic

Copolymers of variable sizes and percent loading

- Copolymer arm length and percent loading are both customizable

Drug Cargo

(Diverse payloads with varying biophysical properties)

Small molecules

Macrocycles

Peptides

Oligonucleotides

Each drug cargo has a customizable release rate (t½) of 5 days, 10 days, 20 days or 30 days

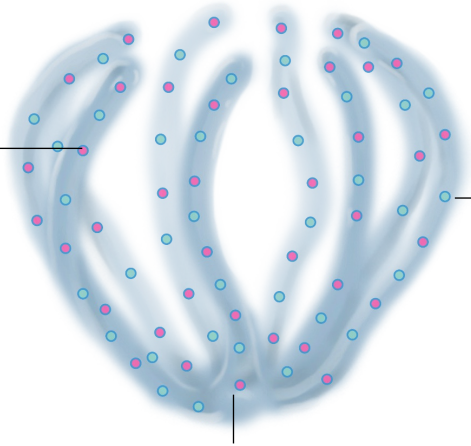
If you can imagine it, we can design it and manufacture it

A single molecule designed to target NLRP3, the driver of neuroinflammation that causes optic neuropathy *and* elevated IOP simultaneously

Glaucoma "Duet": Biopolymer with 2 Small Molecules
NLRP3 inhibitor + IOP lowering agent

Disease Modifying NLRP3 Inhibitor

Targets the underlying neuroinflammation that drives optic neuropathy. May also provide additional IOP lowering effects through TM modulation



IOP Lowering Small Molecule

Extended Durability

A high molecular weight, phosphorylcholine-based biopolymer that enables extended ocular residence time for the potential of a **quarterly dosed intravitreal therapy**

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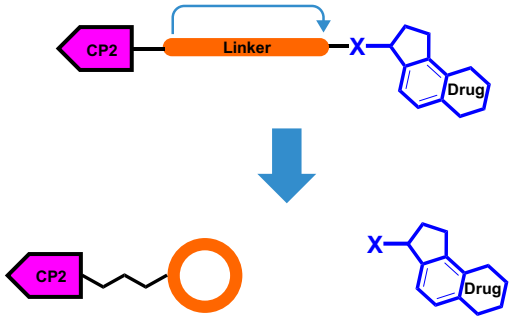
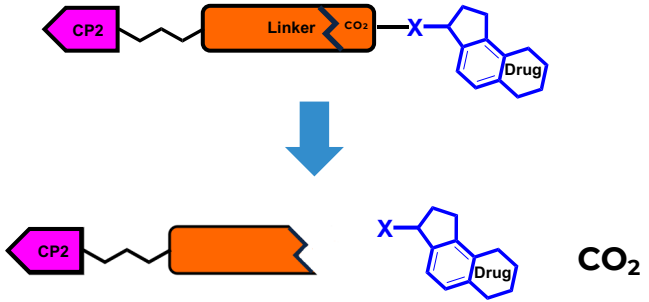
Administered via intravitreal injection

Tunable pH releasable linkers for intravitreal uses

Class 1: Cyclization-Release



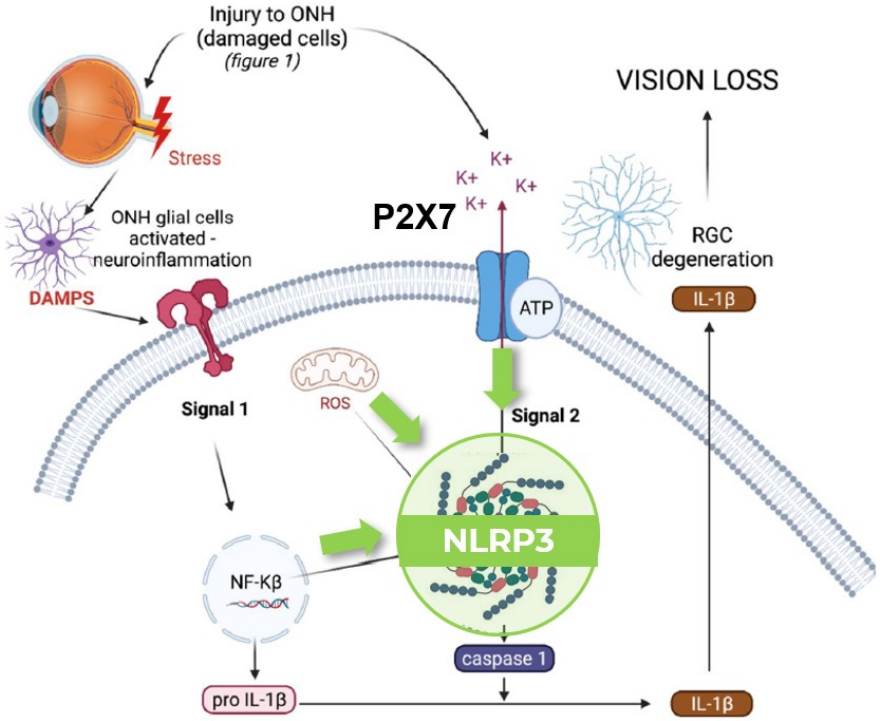
Class 2: Eliminative Release



- Neutral-pH self-immolative linker for IVT
  - The vitreal environment has near-neutral pH and low enzyme levels; therefore, we deploy neutral-pH–responsive self-immolative linkers.
- Release-rate control - SAR demonstrates broad tunability of the linker release half-life ($t_1/_2$) via:
  1. Electronic effects: introducing electron-withdrawing or electron-donating groups to shift local pK_a and modulate fragmentation.
  2. Sterics: using differently hindered groups to accelerate or slow the self-immolation cascade.
- Dosing objective
  - Kinetics can be engineered to support the desired injection interval
- Payload specific
  - The linkers are selected for NLRP3 inhibitors and IOP-lowering agents

NLRP3 Small Molecule Development for Ocular Delivery

The NLRP3 inflammasome complex is a key driver of neuroinflammation that results in optic neuropathy



The NLRP3 inflammasome drives retinal ganglion cell (RGC) degeneration and axon loss[1]

- First, stress to the optic nerve head activates the NF-κB pathway, upregulating NLRP3 and the production of pro-IL-1β
- Second, ATP from damaged cells or reactive oxygen species (ROS) result in NLRP3 inflammasome complex formation, activation of caspase-1, and IL-1β activation by cleavage, leading the RGC degeneration

1. Coyle S, et al. Targeting the NLRP3 Inflammasome in Glaucoma. Biomolecules. 2021 Aug 19;11(8):1239. doi: 10.3390/biom11081239. PMID: 34439904; PMCID: PMC8393362.

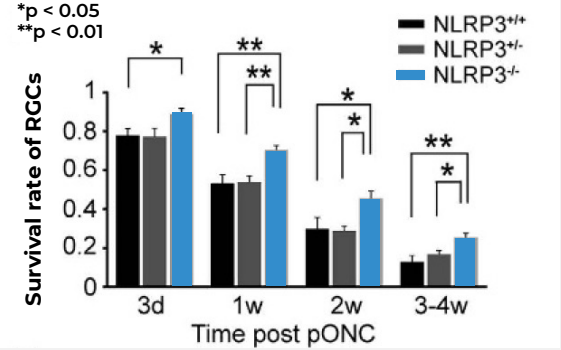
Evidence from animal models support NLRP3 inflammasome driving optic neuropathy, as evident by RGC degeneration and axon loss

- Following an optic nerve crush (pONC), NLRP3 was upregulated in retinal microglial cells. Activation of NLRP3-ASC inflammasome led to the up-regulation of caspase-1 and IL-1β

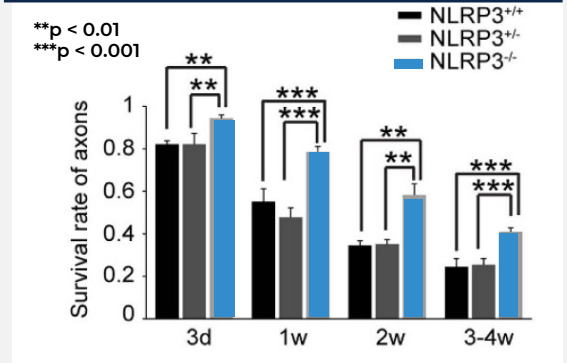
In NLRP3 knockout mice:

– Up-regulation of ASC, caspase-1, and IL-1β were all reduced, and RGC and axon loss was substantially reduced and delayed following pONC injury

More RGCs survived in NLRP3–/– mice than in controls



Survival rate of axons in NLRP3 -/- was much higher than in controls



Puyang, Z., Feng, L., Chen, H. *et al.* Retinal Ganglion Cell Loss is Delayed Following Optic Nerve Crush in NLRP3 Knockout Mice. *Sci Rep* **6**, 20998 (2016). https://doi.org/10.1038/srep20998

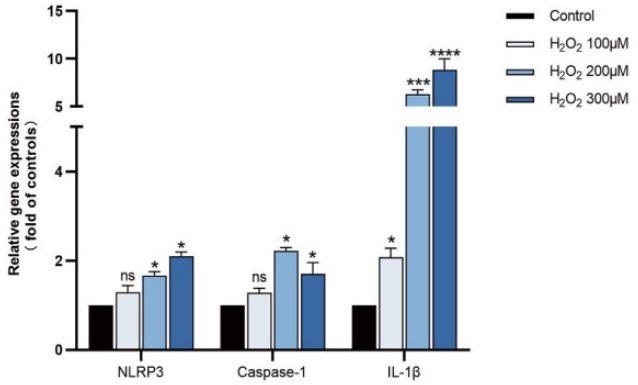
Inhibiting NLRP3 has demonstrated the potential to modulate the trabecular meshwork and lower IOP

- The trabecular meshwork (TM) plays a crucial role in maintaining the aqueous outflow pathway

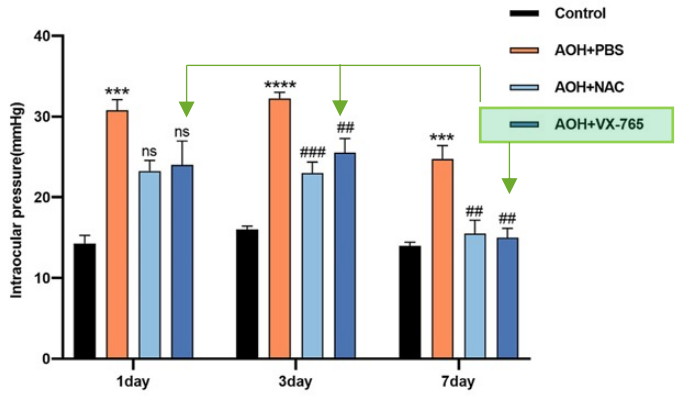
Preclinical studies demonstrated that inhibiting NLRP3/caspase-1 pathway protects the TM and lowered IOP

- Elevated levels of NLRP3 and Caspase-1 were found in TM samples from glaucoma patients
- Oxidative damage in human TM cells led to upregulation of NLRP3, caspase-1, and IL-1β, resulting in decreased cell viability
- Caspase-1 inhibitor VX-765 has been shown to protect TM cells from pyroptosis (cell death) and lowered IOP in rat acute ocular hypertension model

NLRP3, caspase-1 and IL1β mRNA levels are elevated in TM with oxidative stress



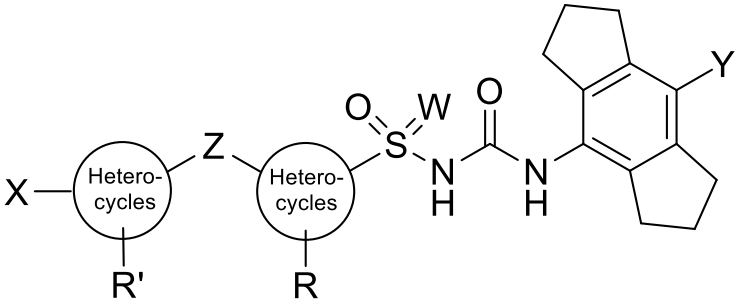
Treatment with VX-765 improved elevated IOP due to AOH

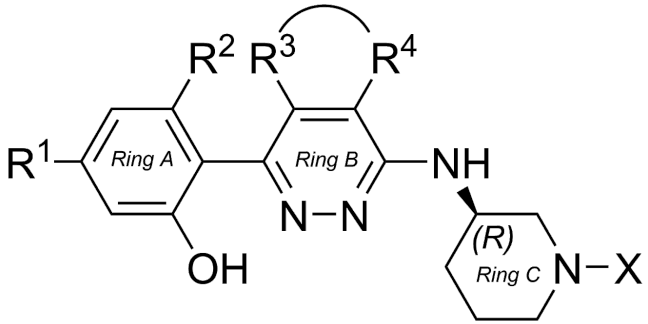


*P < 0.05, **P < 0.01, ***P < 0.001 vs. control, ## P < 0.01, ### P < 0.001 vs. AOH

Feng, Xiaomei et al. Role for NLRP3 inflammasome-mediated, Caspase1-dependent response in glaucomatous trabecular meshwork cell death and regulation of aqueous humor outflow. Heliyon, Volume 10, Issue 19, e38258

Considerations for small molecule NLRP3 inhibitors developed for intra-ocular delivery

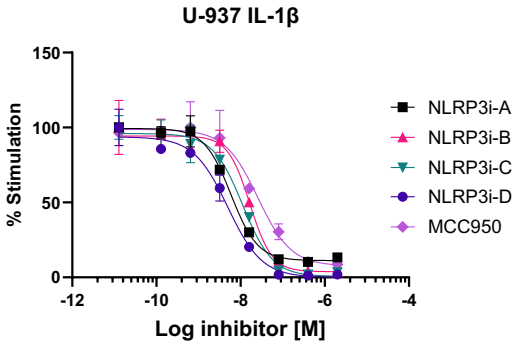




- Across both series, we have multiple examples achieving single-digit nM IC50 in the THP-1 cell IL-1β release assay.
- Conjugation handle:
  - Substitutions on the scaffold end provide a versatile handle for conjugation to ABCD.
- Intravitreal (IVT) delivery vs. systemic NLRP3 inhibitors—focus shifts to ocular
  - Compared with systemically dosed NLRP3 inhibitors, IVT dosing yields low systemic exposure and a wider systemic safety margin.
  - Oral availabilities and BBB properties are no longer major constraints

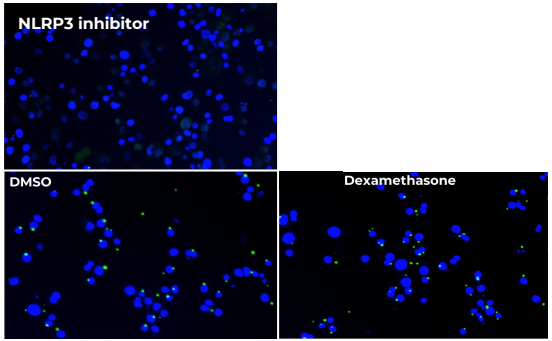
Kodiak's novel small molecule NLRP3 inhibitor candidates decrease IL-1β production and reduce inflammasome complex formation in preclinical studies

NLRP3 inhibitors decrease macrophage IL-1β production in multiple human macrophage lines*



* U937 cells were treated with NLRP3 inhibitors and nigericin activation to monitor IL-1b production

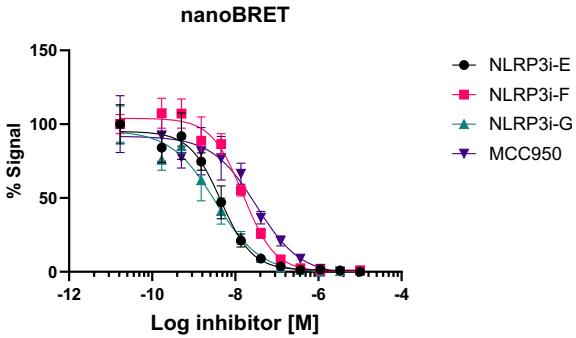
NLRP3 inhibitors reduce inflammasome complex formation



- NLRP3 inhibitors, but not the anti-inflammatory steroid dexamethasone, decreased detectable fusion protein complexes

THP-1 cells expressing GFP-ASC fusion protein were differentiated, primed, compound treated and activated (green)

Inhibitors directly affect NLRP3 molecular interactions†



† Compounds dose-dependently displace a small molecule tracer that promotes the inactivate conformation of NLRP3 in cells

https://kodiak.com/wp-content/uploads/sites/4/2024/05/22.-2024-ARVO-NLRP3-Cell-Assays.pdf
Kodiak Sciences. Investigative Ophthalmology & Visual Science June 2024, Vol.65, 2208.

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Data from tarcocimab, Kodiak's lead ABCD Platform-Based Medicine in Clinic

Challenges in intracellular NLRP3 inhibition: limitations of small molecule delivery to retinal and optic nerve targets using today's technology

Limitations of small molecule delivery

Eye drops

Poor patient compliance and insufficient drug concentration reaching target tissues, such as RGCs and the optic nerve

Orally

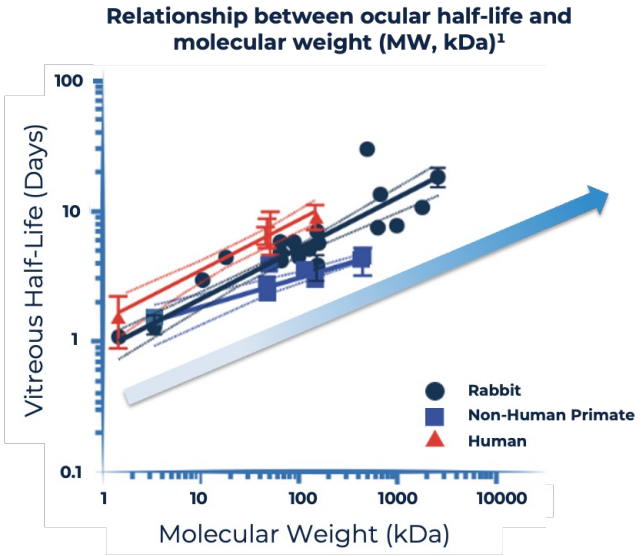
Poor ocular bioavailability and systemic side effects

Intravitreally

Small molecules are cleared quickly from the eye, limiting their efficacy

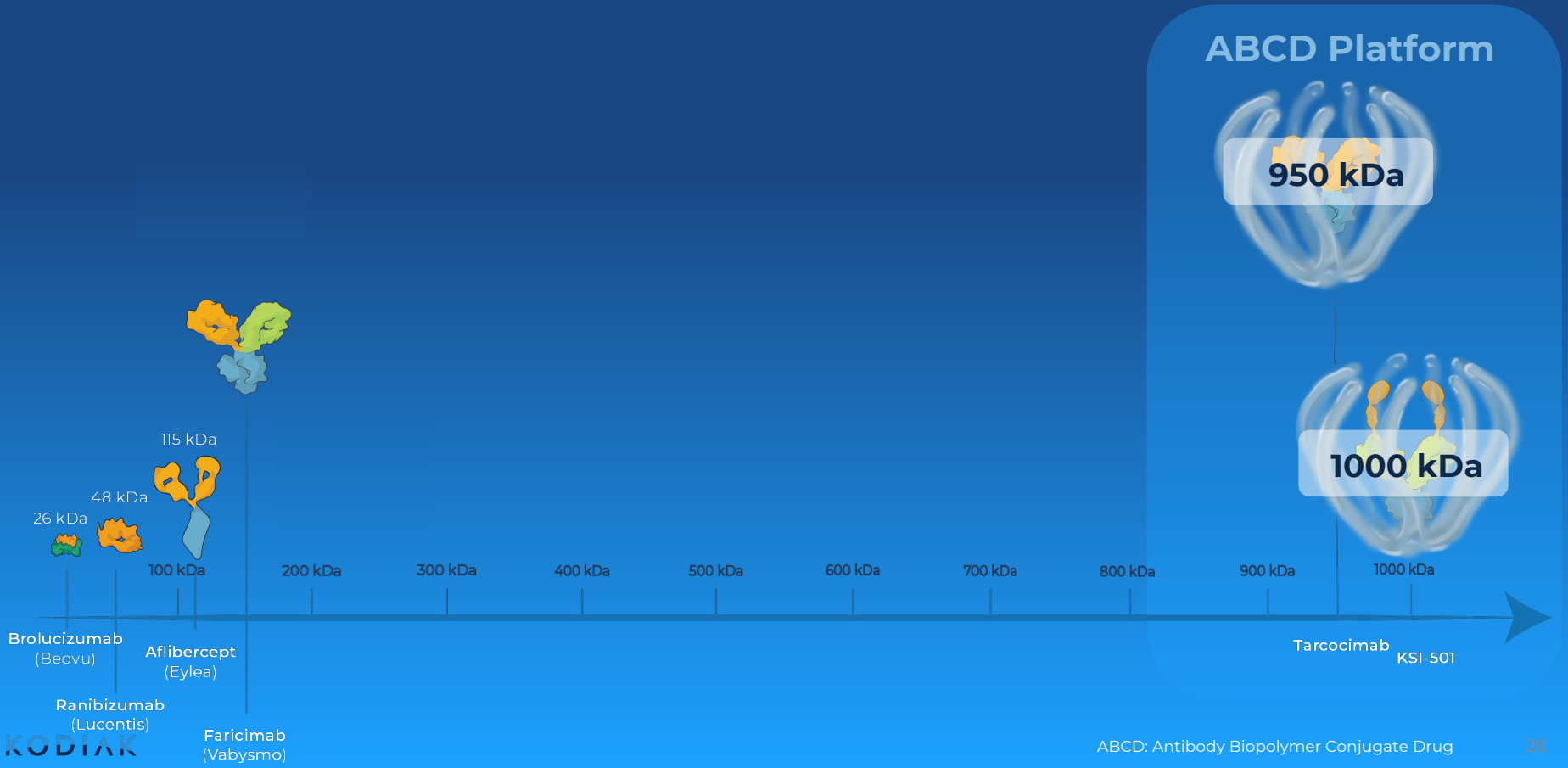
What if we can create an intravitreally injected small molecule that does not clear the eye quickly?

- There is a strong positive correlation between ocular half-life and molecular size for intravitreally injected biologics



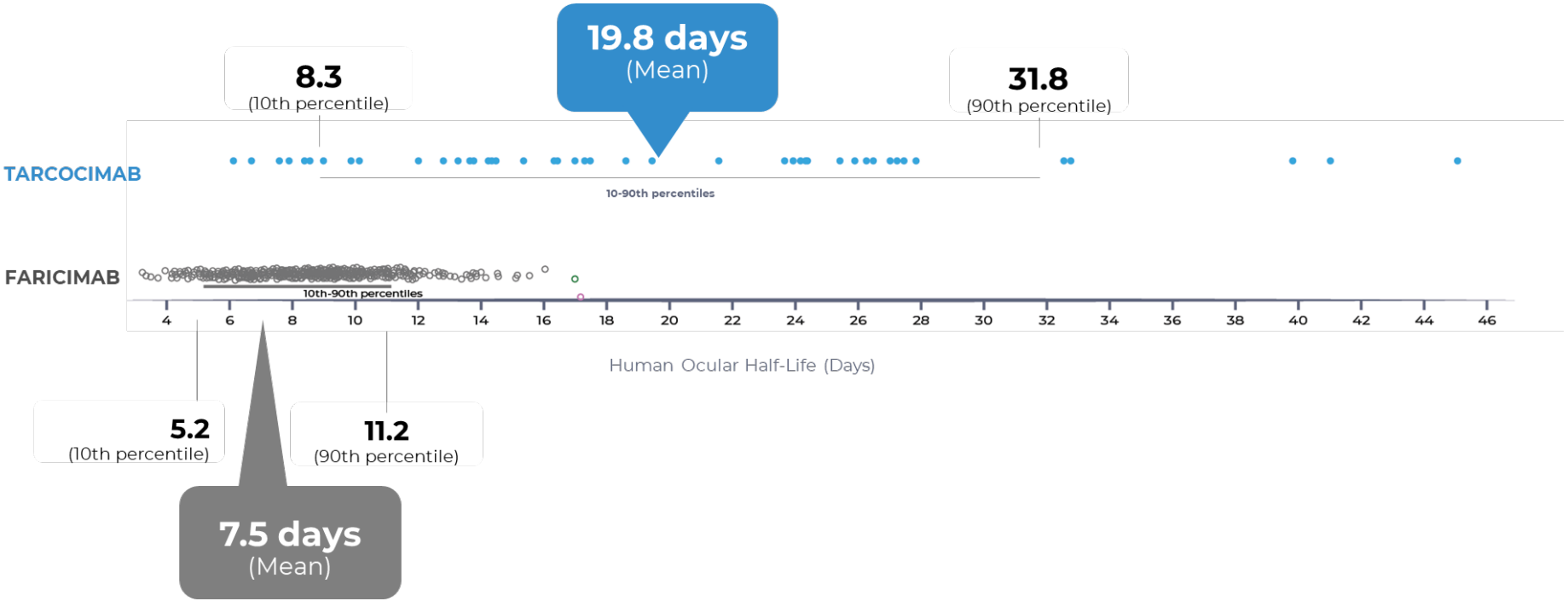
1. Adapted from Crowell SR, et al. Trans Vis Sci Tech. 2019;8(6):1.

Empowered for durability, Kodiak's high molecular weight ABCD Platform offers a unique approach to overcome the limitations of small molecule delivery to the eye



ABCD: Antibody Biopolymer Conjugate Drug

Tarcocimab and the ABCD Platform's high molecular weight increases its human ocular half-life, extending its therapeutic benefit in the eye



Each dot represents the ocular half-life from one individual patient. Blue dots are tarcocimab from the Phase 1b study of tarcocimab in patients with wet AMD, DME and RVO. Gray dots are faricimab from Genentech, Inc. PK and ER of faricimab, Report # 1105763

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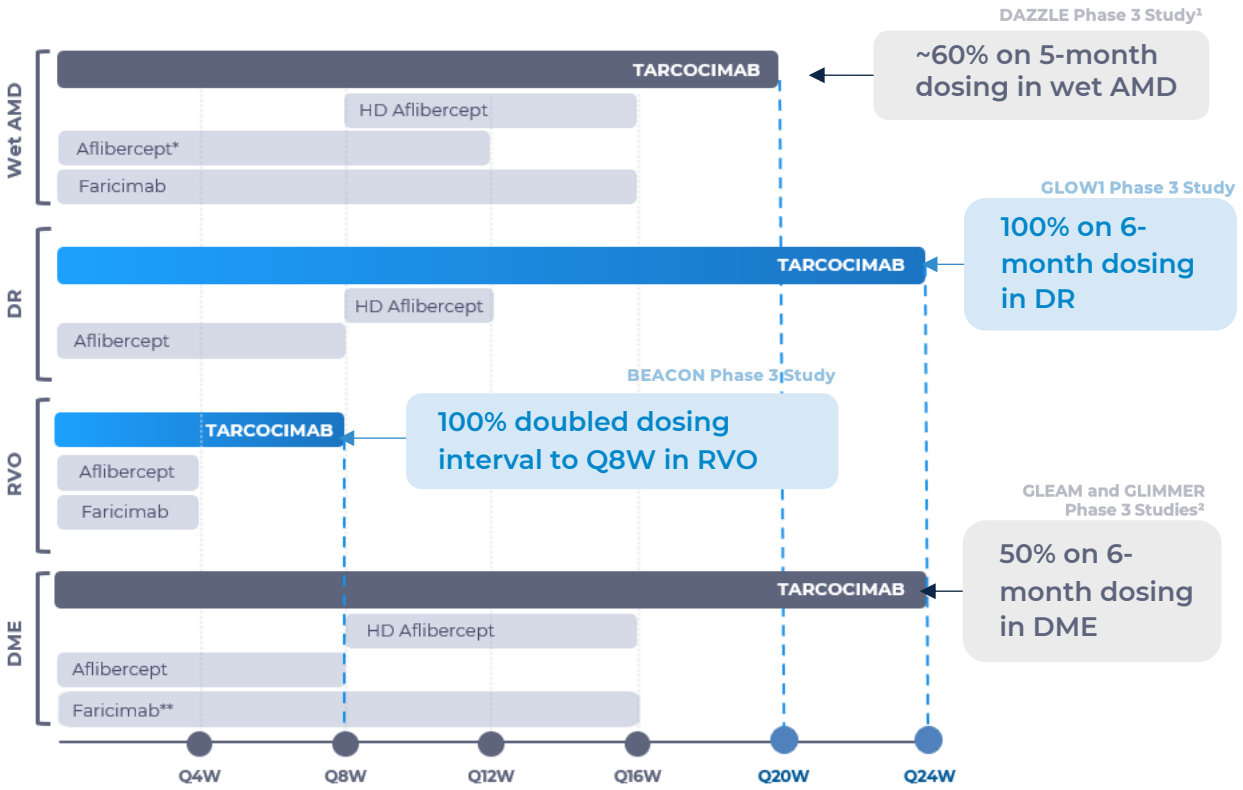
Tarcocimab consistently demonstrated extended durability in multiple retinal vascular diseases across its pivotal studies

- Durability remains a key unmet need in retinal vascular diseases
- **Tarcocimab and the ABCD Platform demonstrated extended durability** compared to today's approved therapies across multiple indications
- **Favorable safety profile also demonstrated with 2,500+ patient years of experience and >13,000 injections**

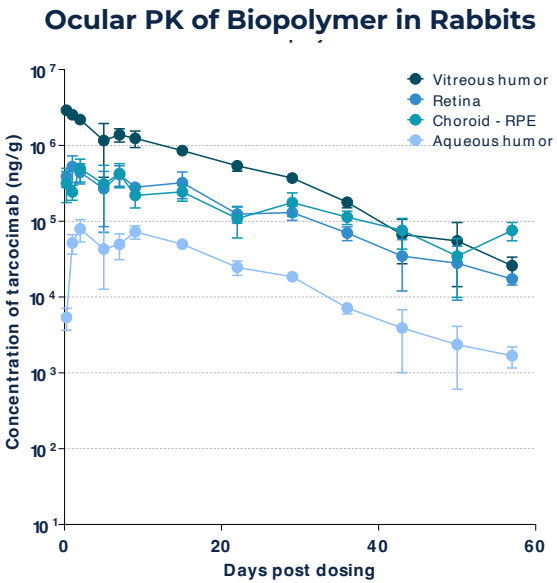
*Q12W after 1 year of effective therapy.
**Based on dosing interval at primary endpoint at year 1 in pivotal studies YOSEMITE and RHINE



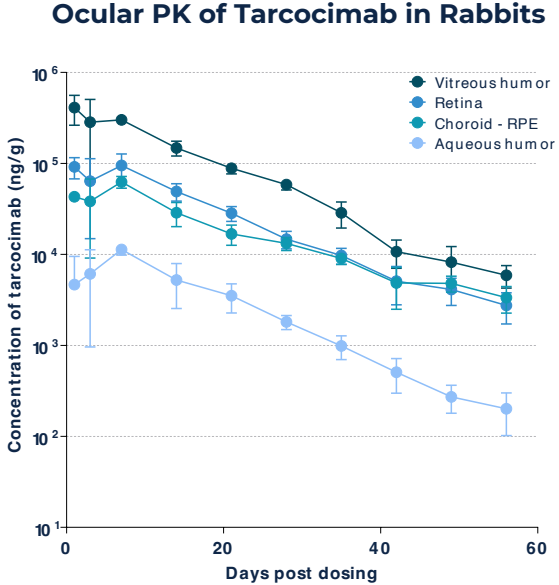
1. Study did not meet primary endpoint believed to be due to the undertreatment of a minority of patients.
2. Studies did not meet primary endpoints due to an unforeseen increase in cataracts in tarcocimab-treated patients; Kodiak's enhanced formulation may mitigate this liability.

Biopolymer selection for glaucoma duet: choosing a biopolymer with similar size to that used in tarcocimab, demonstrating comparable ocular half-life and pharmacokinetics

Biopolymer Alone



Biopolymer + Antibody



Rabbit Ocular Half-Life

Biopolymer	Tarcocimab
11.6	11.1*

(Days)

*Translates to a human ocular half-life mean of ~20 days

In summary, ABCD Platform-based glaucoma “duet” is designed to address 4 key attributes needed in a next-generation glaucoma therapy

Design attributes of the ABCD Platform-based glaucoma “duet”

Neuroprotective

- Glaucoma is an optic neuropathy driven by neuroinflammation
- The **NLRP3 inhibitor** targets the NLRP3 inflammasome complex that drives neuroinflammation causing optic neuropathy

+

Reduces IOP

- The **IOP lowering agent** addresses the IOP elevation stressor
- The NLRP3 inhibitor demonstrates the potential to provide *additional* IOP reduction effects

+

Durable

- The ABCD Platform has a **high molecular weight to increase its ocular half-life**, providing potential for a quarterly dosed intravitreal therapy
- Tarcocimab, an ABC Platform-derived biologic, demonstrated a strong durability profile across multiple pivotal studies

+

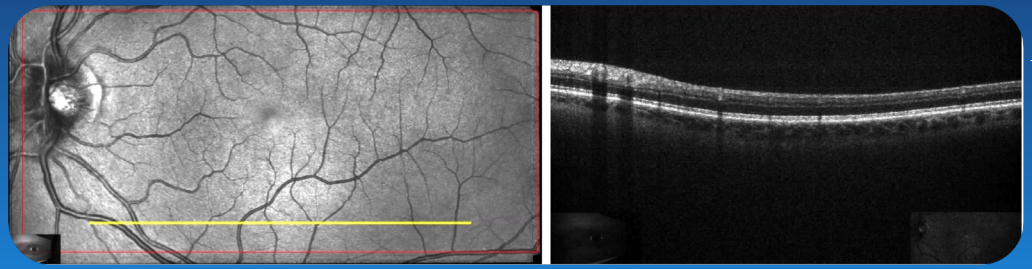
Safe

- Tarcocimab and the ABCD Platform have demonstrated a **favorable safety profile across multiple pivotal studies (>13,000 intravitreal injections)**

VETi Kodiak's digital health innovation for trials and commercial use

high accuracy, frequent testing, patient engagement

Retinal images by VETi

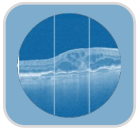


VETi + tarcocimab for home monitoring

VETi + AI

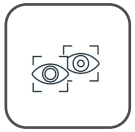
Many applications

Ophthalmology

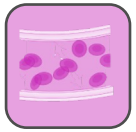

Fluid Analysis


DRSS Scoring


Glaucoma Analysis


Pupillometry

Neuro/Cardio


Metabolic Analysis


Blood Oxygen


Parkinson's Analysis


Alzheimer's Analysis

Consumer


Train Your Brain

Visual Acuity


Biological Age


Train Your Vision

Government


Population Health

KODIAK

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THANK YOU

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